



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

- L (1996) *Nepoviruses: Comoviridae*. In: *Viruses of Plants*, p. 37. Wallingford: CAB International.
- Goldbach R, Martelli GP and Milne RG (1995) Genus *Nepovirus*. In: Murphy FA, Fauquet CM, Bishop DHL *et al* (eds) *Virus Taxonomy – The Classification and Nomenclature of Viruses: Sixth Report of the International Committee on Taxonomy of Viruses*, p. 341. Vienna: Springer-Verlag.
- Martelli GP and Taylor CE (1989) Distribution of viruses and their nematode vectors. *Adv. Dis. Vector Res.* 6: 151.
- Mayo MA and Robinson DJ (1996) *Nepoviruses: molecular biology and replication*. In: Harrison BD and Murrant AF (eds) *The Plant Viruses*, vol. 5, p. 139. New York, London: Plenum Press.
- Mayo MA, Robertson WM, Legorboru FJ and Brierley KM (1994) Molecular approaches to an understanding of the transmission of plant viruses by nematodes. In: Lamberti F, De Giorgi C, Bird DMcK (eds) *Advances in Molecular Nematology*, p. 277. New York and London: Plenum Press.
- Mayo MA, Berns K, Fritsch C *et al* (1995) Satellites. In: Murphy FA, Fauquet CM, Bishop DHL *et al* (eds) *Virus Taxonomy – The Classification and Nomenclature of Viruses: Sixth Report of the International Committee on Taxonomy of Viruses*, p. 487. Vienna: Springer-Verlag.

NERVOUS SYSTEM VIRUSES

Richard T Johnson, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Copyright © 1999 Academic Press



Introduction

Most viral infections of the nervous system represent serious and potentially life-threatening complications of systemic viral infections. With the possible exception of rabies, viruses are not neurotropic in the literal sense of having a specific affinity for the nervous system. Some viruses frequently invade the nervous system yet seldom cause serious disease; for example, mumps virus may cause meningitis but even during uncomplicated mumps parotitis cerebrospinal fluid changes in over 50% of patients indicate probable nervous system infection. Other viruses, such as herpes simplex virus, rarely infect the central nervous system; but when they do, they often cause fatal disease. Thus both mumps and herpes simplex viruses are regarded as neurotropic; mumps is highly neuroinvasive but has limited neurovirulence; herpes simplex has low neuroinvasiveness but is highly neurovirulent. Such variations are dependent on the structural and functional determinates of nervous system invasion, on the particular neural cells which specific viruses infect, on the effect of this infection on the host cells, and on the immune response or immunopathologic responses to the infection. Several terms need definition:

- **Neurotropic:** able to infect neural cells;
- **Neuronotropic:** able to infect neurons in contrast to other nervous system cells;
- **Neuroinvasive:** able to enter the nervous system;

- **Neurovirulent:** able to cause neurologic disease.

Anatomic Considerations

Both structural and functional features of the central nervous system present a unique milieu for viral replication. The blood–brain barrier and the compact structure of the brain and cord pose formidable barriers to the entry or dissemination of viruses within the nervous system. Furthermore, neurons are unique cells with high metabolic rates, intense membrane specialization, and no regenerative capacity. The same barriers that exclude viruses also limit access of immunocompetent cells and antibodies, and the nervous system lacks an intrinsic lymphatic system and has a paucity of phagocytic cells. Thus, the barriers that inhibit virus invasion also deter viral clearance. Therefore, many persistent infections involve the central nervous system.

The blood–brain barrier was originally conceptualized from the observation that dyes, such as trypan blue, stain all tissues except the brain and spinal cord after injection into the systemic circulation. The barrier at the cerebral capillary level consists of tight junctions between the capillary endothelial cells (beyond which most dyes do not pass), a dense basement membrane around the cells and tightly opposed astrocytic footplates. In the choroid plexus, the blood–cerebrospinal fluid barrier is structurally different. The capillaries of the plexus are fenestrated,

lack a basement membrane and are surrounded by a loose stroma. Dyes and particles readily pass into the choroid plexus but are prevented from entering the cerebrospinal fluid by tight junctions located at the apices of the secretory epithelial cells of the choroid plexus. Tight junctions between the arachnoid cell over the surface of the brain complete the barrier.

There is no comparable barrier between the brain and the spinal fluid. The ependymal cells are not joined by tight junctions and, therefore, there is a free exchange between the extracellular space of the brain and the cerebrospinal fluid. The bulk flow is centrifugal, however, and solutions in the cerebrospinal fluid have limited entry into central nervous system tissue in normal circumstances. Furthermore, the intracellular gap between neural cells measures only 10–15 nm, less than the diameter of even the smallest virus, so that free movement of virus particles or inflammatory cells within the extracellular space is relatively restricted.

Neurons have specialized membranes for the transmission and receipt of specific messages; they also have axonal extensions to carry signals to and from distant neuronal populations, motor endplates, and sensory endings. In humans these cytoplasmic extensions may exceed a meter in length. These features are important in viral infections, since different subpopulations of neurons have different receptors usurped by viruses to permit entry into cells. Furthermore, viruses in some cases can be carried by axoplasmic transport systems either into the nervous system or within the nervous system where axonal processes link functionally related neurons. The high metabolic rates and lack of regenerative capacity may be important in chronic noncytopathic infections. A generalized infection that deranged cellular metabolism or caused shortened cell survival might present as a neurological disease and might have pathological findings restricted to the nervous system. Lack of neuronal replacement also assures that latent infection of neurons confers lifelong persistence in the host.

Antibodies found in the normal central nervous system are derived entirely from the serum. Antibody levels of immunoglobulin G (IgG) are approximately 0.4% of the serum levels. Since diffusion of macromolecules across the barrier is largely size dependent, immunoglobulin M (IgM) is present in even lower levels. Complement is largely excluded. When inflammation disrupts the blood–brain barrier, antibody molecules leak into the nervous system along with other serum proteins. When a mononuclear inflammatory response is mounted against infection, T lymphocytes usually enter the nervous system first followed by macrophages and B lymphocytes. These

B cells from the peripheral circulation move into the perivascular space and can generate immunoglobulins intrathecally.

Pathways of the Central Nervous System Invasion

Viruses have been shown to enter the nervous system both along nerves and from the blood. The first experimental studies of viral invasion employed rabies, herpes simplex or polioviruses, all of which under experimental circumstances can penetrate the nervous system along peripheral nerves. The precise mechanism of neural spread remained a mystery for many years, since it was thought that the axoplasm slowly oozed in an anterograde direction. It was proposed that virus might move in perivascular lymphatics, by ascending infection of the supportive cells within the peripheral nerve, or even by replication in axons; a speculation that is now untenable because of the observed lack of ribosomes or protein synthesis within axons. In the 1960s active anterograde and retrograde axon transport systems were found. Viruses or other particles can be taken up in vesicles at the nerve terminals and transported to the cell body of the sensory or motor neuron (Fig. 1). This neural route of entry is important in primary viral infections such as rabies and possibly poliomyelitis. Retrograde transport also moves herpes simplex and varicella-zoster viruses from mucous membranes or skin into sensory ganglia at the time of primary infection. Subsequently, anterograde transport carries the reactivated virus from the ganglia to the periphery during exacerbations. Anterograde transport of herpes simplex virus by nerves innervating the dura from the trigeminal ganglia may explain the unique temporal lobe localization of herpes simplex virus encephalitis.

The olfactory spread of virus is a variation of neural spread. In the olfactory mucosa neural fibers provide a unique pathway; the apical processes of receptor cells extend beyond the free surface of the epithelium as olfactory rods and the central processes synapse in the olfactory bulb. These are the only nerve cells with processes that link the central nervous system and the ambient environment. Indeed, some colloidal particles placed on the olfactory mucosa can be found in the olfactory bulbs within 1 h. Experimental studies show that viruses can enter through this route, and this may occur in some aerosol infections in humans such as laboratory accidents or rabies virus infections in bat-infested caves. Also the olfactory pathway has been postulated as a possible route of herpes simplex virus entry into the nervous system as an alternate explanation for the orbital-

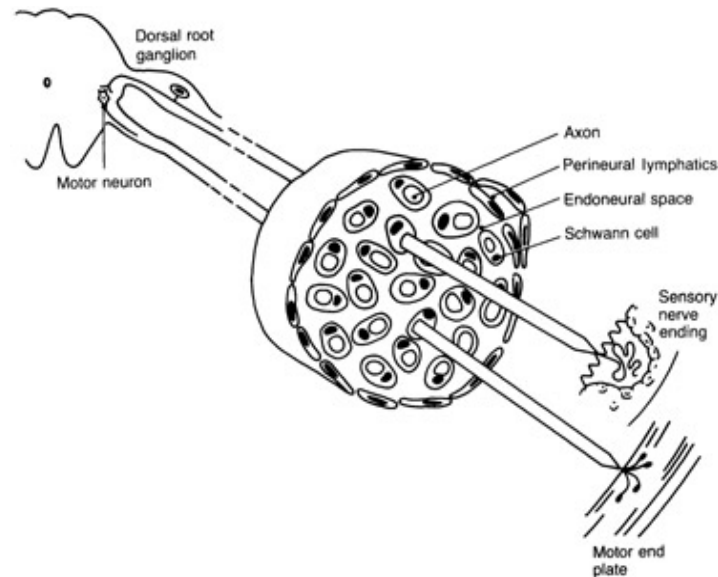


Figure 1 Schematic diagram of possible routes of neural spread of viruses to the nervous system. (Reproduced with permission from Johnson RT (1982) *Viral Infections of the Nervous System*, New York, Raven Press.)

frontal and medial temporal lobe localization of herpetic encephalitis. Nevertheless, despite the apparent ease of spread along this route, it appears to be a rare route of natural infection.

In most experimental and natural infections, viruses invade the brain from the blood. Historically, the blood-brain barrier was believed to be impervious to viruses. This belief was based in part on the fact that viruses experimentally inoculated directly into brain cause disease after a brief inoculation period, whereas the incubation period after intravenous inoculation is longer and comparable to that following cutaneous or peritoneal inoculation. The reason for this delay in infection is that virus in the blood is rapidly removed by the reticuloendothelial system; therefore, intravenous inoculation is, in fact, an inoculation primarily of the Kupffer cells of the liver and other reticuloendothelial cells. Therefore, virus must establish a nidus of peripheral replication that can effectively seed a viremia of sufficient magnitude and duration to allow invasion across the blood-brain barrier (Fig. 2). Thus, some viruses grow in lymphatics and seed into the blood directly via the thoracic duct, others grow in vascular epithelial cells, and others replicate in highly vascular tissue such as muscle.

A persistent viremia can be achieved by several mechanisms. Rate of clearance is dependent upon particle size; small particles such as togaviruses and flaviviruses can maintain high titer plasma viremias with sufficient rapid replication in peripheral tissue. Other viruses adsorb to red blood cells and thus evade clearance. Many large viruses such as measles and

herpesviruses infect white blood cells thus evading clearance and replicating at the same time.

Some viruses enter the nervous system across the capillary endothelium and others across the choroid plexus. Some viruses infect the capillary endothelial cells and simply grow into the brain while others are able to transit across endothelial cells despite their paucity of endocytotic vesicles. Entry in infected leukocytes is a theoretical possibility but leukocyte traffic into the nervous system is limited, although trauma or inflammation due to other causes may predispose the nervous system to infection with viruses that infect white blood cells. Although there are areas of increased blood-brain barrier permeability, no viral infection has been shown to selectively infect these areas. Other viruses, such as mumps virus, grow in choroid plexus epithelium and seed into cerebrospinal fluid. Thus, the clearance of particles by the reticuloendothelial system, barriers of non-susceptible extraneural cells, production of interferon and other nonspecific inhibitors, and the physical barriers of the nervous system itself probably explain why viral infections of the brain are rare, even though systemic infections with the potential pathogens are very common.

Infection of Neural Cells

Once a virus has penetrated into the nervous system it must contact a susceptible cell and spread through the compact neuropil which is a theoretical problem. The fact that some viruses can be neutralized by extra-

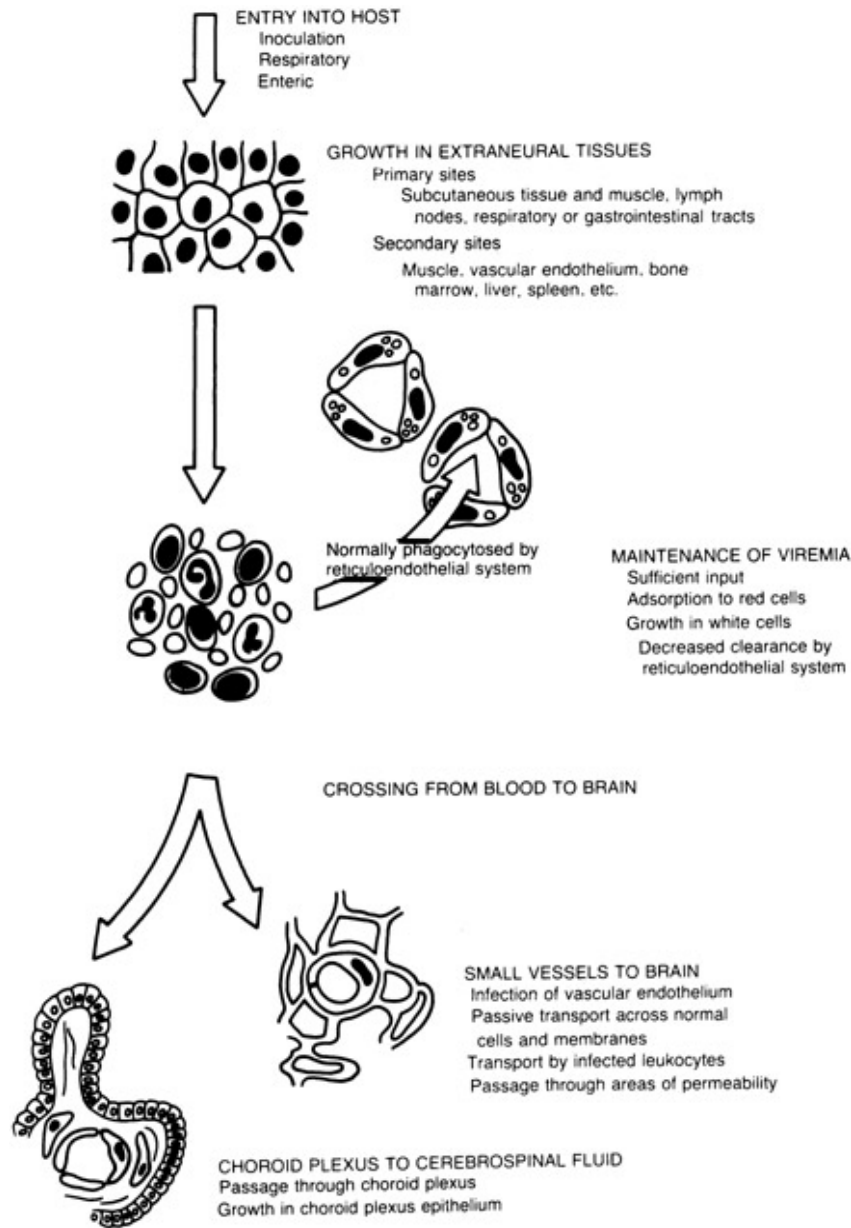


Figure 2 Schematic diagram of steps in the hematogenous spread of viruses to the nervous system. (Reproduced with permission from Johnson RT (1982) *Viral Infections of the Nervous System*, New York; Raven Press.)

cellular antibody even after central nervous system invasion shows that viruses such as togavirus and flaviviruses do spread in extracellular space, but this is not true of larger viruses. Conversely, the compact neuropil may facilitate the contiguous cell-to-cell spread of viruses. For example, in subacute sclerosing panencephalitis, a chronic brain infection of humans with measles virus, extracellular, enveloped virus is never seen, and there are enormous titers of extracellular antibody. Apparently the fusion protein allows measles virus to move from cell to cell through the brain.

Cell-to-cell spread may also involve axoplasmic transport causing infection of functionally linked cells; for example, in poliovirus infections the virus is rapidly spread through the motor system. Some viruses infect only neuronal populations such as rabies, polioviruses, and the arthropod-borne viruses, and some only infect selective neuron populations. Other viruses, such as herpes simplex virus, appear to infect neurons and glial populations with little selectivity.

Infection limited to vascular endothelial cells is found with rickettsial infections but is not recognized

in any viral infection of the nervous system. Infection limited to choroid plexus and meningeal cells appears to occur with those viruses that cause benign meningitis. In experimental studies with a number of viruses, widespread lytic infection of ependymal cells can lead to closure or stenosis of the aqueduct of Sylvius and resultant hydrocephalus. Similar aqueductal stenosis and hydrocephalus has been described in children after mumps virus meningitis.

The selective infection of oligodendrocytes has been recognized in nature in the disease progressive multifocal leukoencephalopathy caused in humans by the JC virus and in monkeys by SV-40 virus. In the course of immunosuppression, now seen most frequently with acquired immunodeficiency syndrome (AIDS), a selective lytic infection of oligodendrocytes causes multifocal areas of demyelination in the brain.

With changes in age, the specificity of infection and vulnerability of neural cells may change. For example, bluetongue virus infection of fetal sheep destroys the precursors of neurons and glia of the subependymal plate which leads to hydranencephaly or porencephaly depending on the age of fetal development, whereas the virus fails to infect the mature post-migratory cells in the late gestational or postnatal animal. Similarly, the external granular cells of the cerebellum in fetal or newborn animals are selectively infected by parvoviruses, and destruction of these mitotic cells leads to the granulo-prival cerebellar degeneration seen in both natural and experimental animal infections.

Mechanisms of Cell Damage

Viral infection can have diverse effects on the host cell.

- Virus products may disrupt the integrity of the plasma membrane of the cell causing cell lysis.
- Infection with many viruses activates programmed cell death or apoptosis. This process of cell elimination is important in embryonic development, normal cell turnover, immunocyte clone deletion and other homeostatic processes but is particularly important in the nervous system, where massive cell elimination takes place during sculpting of the brain and cord and tight inhibition of apoptosis of mature neurons is required since they have no replicative capacity. This activation of death suppressor genes has explained the age-dependent effects of some neurotropic viruses.
- Virus genes or gene products may accelerate or inhibit host cell growth rate or can transform the cell so that it lacks contact inhibition.
- Infection can alter the antigenic composition of the cytoplasmic membrane making the cell the target of cytotoxic T cells and autoimmune cell lysis. This is the process that causes acute meningoencephalitis and death in mature mice infected with lymphocytic choriomeningitis virus.

Noncytopathic infections of neural cells also occur and lead to persistent infection with no disease or disorders without obvious histological changes. For example, neuroblastoma cells in culture infected with noncytopathic viruses such as rabies can show normal morphology, growth rates and protein synthesis, but reduced synthesis of specific neurotransmitters or receptors. These have been termed 'luxury functions', although *in vivo* the ability of neurons to synthesize transmitters or receptors would hardly be considered a luxury. Analogous noncytopathic infection has been demonstrated in mice congenitally infected with lymphocytic choriomeningitis virus. Congenitally infected mice are usually 'runts', but studies have shown selective infection of cells of the anterior pituitary that normally generate growth hormone. The animals are actually pituitary dwarfs responsive to growth hormone therapy.

Indirect cell damage can occur in viral infections that lead to sensitization of the host to neural antigens. This has been demonstrated in rats infected with coronaviruses, where the infection of neural cells leads to a cell-mediated autoimmune response to myelin proteins and to subsequent demyelination that can continue in the absence of ongoing infection. In postmeasles encephalomyelitis of humans, autoimmune demyelination appears to occur in the absence of infection of neural cells. Infection of lymphoid tissue leads to disruption of normal immune regulation, and about 1 per 1000 persons develop a symptomatic autoimmune reaction to myelin basic protein.

Other indirect mechanisms of neural cell damage have been postulated to explain the diverse neurological diseases seen in the course of human immunodeficiency virus (HIV) infection. The virus does not appear to cause infection of neurons, although neuronal processes and function are altered. The primary cells that are infected are macrophages and the microglia of the brain derived from macrophage populations. Possibly viral proteins produced by these cells or cytokines released by these cells interfere with neuronal function or are toxic to neurons or glial cells. For example, tumor necrosis factor, a lymphokine often elevated in brains of neurological-affected AIDS patients, has been shown *in vitro* to induce demyelination.

Clinical Features

Acute Infections

The varied clinical features of viral infections of the nervous system can be explained in large part by the factors discussed above. Thus, a virus may infect only meningeal or ependymal cells, and cause a clinical syndrome known as viral meningitis or acute aseptic meningitis. This clinical syndrome is characterized by fever, headache and nuchal rigidity secondary to meningeal irritation but without clinical signs suggesting parenchymal disease. The commonest causes of acute viral meningitis are enteroviruses and mumps virus.

Encephalitis is a clinical syndrome in which, in addition to fever, headache and stiff neck, there is paralysis, seizures or other evidence of parenchymal disease of the brain. The commonest causes of severe encephalitis in man are herpes simplex virus and the arthropod-borne viruses. The former infects neurons and glia and causes diffuse necrotizing encephalitis in the newborn, but focal encephalitis in the immune child or adult presumably because diffuse virus spread is contained by immune responses. Focal signs, hallucinations, behavioral abnormalities and aphasia are more common with herpes encephalitis because of the localization to temporal lobes. Arboviruses have a propensity to infect neurons, and some flaviviruses tend to infect basal ganglia and brainstem neurons causing movement disorders and sudden respiratory failure. If signs of spinal cord involvement accompany encephalitis the term encephalomyelitis often is used. However, the term encephalomyelitis is also used to distinguish an acute postinfectious demyelinating disease of assumed autoimmune origin from acute viral encephalitis. Postinfectious encephalomyelitis (or acute disseminated encephalomyelitis) usually occurs 3–14 days after exanthems (measles, varicella or rubella) or respiratory infections (mumps, influenza and others) and clinically is characterized by the abrupt onset of fever, obtundation, seizures and multifocal neurological signs.

The clinical syndromes of rabies and poliomyelitis are the most distinctive of viral infections because of the selective infection of specific populations of neurons. Polioviruses selectively infect motor neurons which leads to flaccid paralysis. Rabies virus infects limbic system neurons with a relative sparing of cortical neurons early in disease leading to behavioral abnormalities. Rabies virus infections represent a diabolical adaptation of virus to animal host, causing the animal to remain alert but to lose timidity and develop aggressive behavior to transmit the virus. The advantage of this selectivity is evident considering

that strains of rabies that cause the so-called 'dumb' or passive rabies are seldom transmitted in nature.

Slow Infections

Slow infections are characterized by long incubation periods of months to years followed by an afebrile progressive disease. The term was originally coined in veterinary medicine to describe several transmissible diseases in sheep. The prototype slow infections are scrapie, a chronic noninflammatory spongiform encephalopathy due to a transmissible agent in which no nucleic acid has been identified (a prion), and visna, a chronic inflammatory encephalomyelitis caused by a lentivirus.

The first slow infections identified in humans was kuru, a progressive ataxia of a tribal group in New Guinea where the agent, resembling the agent of scrapie, was transmitted by ritual cannibalism. Creutzfeldt–Jakob disease, a subacute dementia with myoclonus, is a worldwide disease due to prion agents. In both of these human spongiform encephalopathies the clinical disease progresses irrevocably to death in about six months, but without fever or other clinical or histological findings to suggest infection.

In 10–15% of cases of Creutzfeldt–Jakob disease transmission is genetic resulting from insertions or point mutations in the gene coding for the prion protein. Some of these mutations result in phenotypes resembling sporadic Creutzfeldt–Jakob disease except that onset may be at an earlier age and progression to death may be more prolonged; in other mutations the phenotype is distinctive as in Gertmann–Straussler disease with prominent cerebellar ataxia or familial fatal insomnia where sleep disturbances dominate the early phase of disease. In rare cases, transmission has been iatrogenic with corneal and dural grafts, with neurosurgical procedures and with the injection of pituitary hormones extracted from human cadavers. Recent evidence suggests some cases are transmitted from beef contaminated with bovine spongiform encephalopathy. In the vast majority of cases no abnormality of the prion gene is found, and no common exposure is detected; in 85% of cases the mode of transmission is unknown.

Dementia, a chronic deterioration of cognitive function, is also caused by several conventional viruses. Subacute sclerosing panencephalitis is a chronic dementing illness caused by measles virus. One per million otherwise healthy children develop this chronic illness at an average of seven or eight years after uncomplicated measles. Dementia evolves slowly, associated with myoclonic movements and high levels of measles antibody in serum and cerebrospinal fluid. Children usually die a year or

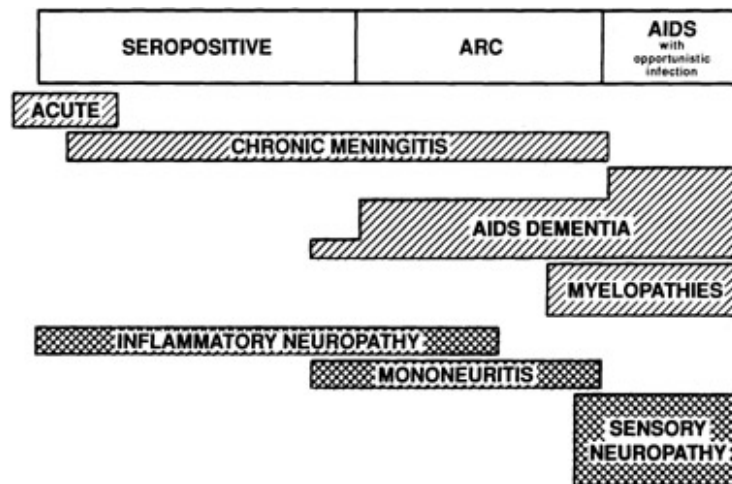


Figure 3 Schematic diagram of human immunodeficiency virus-related neurological diseases. Disease affects central (diagonal lines) and peripheral (cross-hatched lines) nervous systems, evolve at different stages of infection (asymptomatic seropositive, AIDS-related complex [ARC] and full-blown AIDS) and occur at different frequencies (indicated by vertical width). (Reproduced with permission from Johnson RT, McArthur JC and Narayan O (1988) *FASEB J* 2: 2970.)

less after the onset of clinical signs, but survival may vary from six weeks to six years. The disease is due to a subacute, slowly progressive diffuse infection of neurons and glial cells.

Progressive multifocal leukoencephalopathy due to JC virus also evolves as a slow viral infection with a selective infection of oligodendrocytes and a progressive demyelinating disease. Multifocal neurological signs evolve including cognitive dysfunction, paralysis, blindness and disorders of speech. Fever is absent and the cerebrospinal fluid shows no evidence of inflammation. Disease progresses relentlessly to death over a period of months.

Clinical symptoms associated with HIV are very diverse (Fig. 3). This virus now represents the commonest viral infection of the nervous system. From prospective studies of cerebrospinal fluid changes, it appears that the majority of people infected with the virus have early invasion of the nervous system; that is, the virus is highly neuroinvasive. However, early during this infection, neurological disease is rare. A presumed autoimmune disorder occasionally causes a demyelinating peripheral neuropathy (Guillain-Barré syndrome); acute meningitis is occasionally seen at the time of seroconversion or during early asymptomatic infection. An asymptomatic pleocytosis is often found. At this stage therefore, the virus is not highly neurovirulent. However, after the onset of immunodeficiency the infection is neurovirulent; 50% of AIDS patients develop progressive dementia with cerebral involvement, myelopathies or painful sensory neuropathies. The pathogenesis of these complications is unknown, but they are thought to be due to some viral protein or

lymphokine incited by the virus because of the relative paucity of the virus in the nervous system and its localization to the microglial and macrophage populations.

Tropical spastic paraparesis complicating human T cell leukemia virus, type 1, infections is a recently recognized slow nervous system infection. Less than 2% of the patients infected with this virus develop either acute T cell leukemia or neurological disease. Since many of those infected are infected by breast milk and the onset of tropical spastic paraparesis is usually in the fourth or fifth decade of life, the incubation period is extraordinarily long. A subacute disease develops with progressive paralysis of the lower extremities associated with impotence, incontinence and sensory symptoms, but usually minimal sensory findings. Disease progresses slowly until the patients are wheelchair bound, but the disorder remains primarily at the level of the thoracic spinal cord. The involvement of the upper extremities is minimal with hyperreflexia but usually good function, and there is usually little, if any, indication of cerebral involvement. Early pathology in the spinal cord has shown vasculitis. In late stages hyalinization of vessels with necrosis and demyelination of spinal cord are found, and findings are most prominent in the thoracic cord. Whether virus replicates in any cells other than T lymphocytes is still uncertain. These observations lead to the questions of why less than 1 in 100 who are infected develop disease; why the incubation period is as long as 40 years; why the disease localizes to the thoracic spinal cord; and why over years the disease becomes relatively quiescent despite the fact that there are ongoing high levels of

intrathecal antibody synthesis suggesting that there is still antigenic stimulation by virus within the nervous system.

Identification of viruses or virus-like agents (prions) in a variety of chronic neurological diseases has led to speculation of a viral etiology for multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, schizophrenia and other illnesses. Experimental evidence for viruses in these chronic diseases is still tenuous.

See also: Apoptosis and virus infection; Autoimmunity; Encephalitis viruses (*Flaviviridae*); Encephalitis viruses and related viruses causing hemorrhagic disease, Tick-borne encephalitis and Wesselsbron viruses; Enteroviruses (*Picornaviridae*); Animal and related viruses, Human enteroviruses (serotypes 68–71); Herpes simplex viruses (*Herpesviridae*); General features, Molecular biology; Human immunodeficiency viruses (*Retroviridae*); Molecular biology, Anti-retroviral agents, General features; Human T-cell leukemia viruses (*Retroviridae*); HTLV-1, HTLV-2; JC and BK viruses (*Papovaviridae*); Latency; Lymphocytic choriomeningitis virus (*Arenaviridae*); General features, Molecular biology; Measles virus (*Paramyxoviridae*); Mumps virus (*Paramyxoviridae*); Orbiviruses and coltivirus (*Reoviridae*); General

features, Molecular biology; Parvoviruses (*Parvoviridae*); Cats, dogs and mink, Molecular biology, Rodents, pigs, cattle and waterfowl, General features; Pathogenesis: Animal viruses, Plant viruses; Persistent viral infection; Polioviruses (*Picornaviridae*); General features, Molecular biology; Prions: Human and Animal, Yeast and Fungi; Rabies virus (*Rhabdoviridae*); Varicella-Zoster virus (*Herpesviridae*); General features, Molecular biology; Viral receptors; Virus–host cell interactions; Visna-Maedi viruses (*Retroviridae*).

Further Reading

- Glass JD and Johnson RT (1996) Human immunodeficiency virus and the brain. *Ann. Rev. Neurosci.* 19: 1.
 Johnson RT (1998) *Viral Infections of the Nervous System*, 2nd edn. Philadelphia: Lippincott-Raven.
 Levin MC and Jacobson S (1997) HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP): a chronic progressive neurological disease associated with immunologically mediated damage to the central nervous system. *J Neurovirol* 3: 126.
 Prusiner SB (1997) Prion diseases and the BSE crisis. *Science* 278: 245.
 Takahashi K, Wesselingh SL, Griffin DE *et al* (1996) Localization of HIV-1 in human brain using PCR/*in situ* hybridization and immunocytochemistry. *Ann. Neurol.* 39: 705.

NEWCASTLE DISEASE VIRUS (PARAMYXOVIRIDAE)

Peter T Emmerson, Department of Biochemistry and Genetics,
 Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne, UK

Copyright © 1999 Academic Press

History

Newcastle disease was the name given by Doyle to a highly contagious viral infection of poultry, also known as fowl pest, which was first reported on a farm near Newcastle upon Tyne, UK, in 1926. Shortly after the reported disease at Newcastle, two further outbreaks occurred in the UK, one in Somerset and the other in Staffordshire. At about the same time, a disease with similar symptoms was observed in Java (in the city now known as Jakarta), Indonesia, and shortly thereafter in other regions of southeast Asia, notably around seaports of the Indian Ocean. Subsequent crossimmunity tests showed that the viruses

isolated in southeast Asia and Newcastle upon Tyne were indistinguishable. The causative agent of the disease in Newcastle upon Tyne was identified as a virus which was distinct from fowl plague (avian influenza virus), although the symptoms bore some resemblance. It is thought likely that the virus was transported to the port of Newcastle upon Tyne by ship from southeast Asia. Whatever its origin, the new disease emerged or was first recognized in 1926 and rapidly spread throughout the world.

Newcastle disease was first recognized in various countries as a highly pathogenic disease with up to 100% mortality. In California, a relatively mild respiratory disease was first observed in the mid-

